Ritlecitinib (LITFULO) in Alopecia Areata
National Drug Monograph
December 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Ritlecitinib is a dual inhibitor of Janus kinase 3 (JAK3) and the *t*yrosine kinase *e*xpressed in hepatocellular *c*arcinoma (TEC) family of kinases.[i]

Indication Under Review in This Document

- Treatment of severe alopecia areata (AA) in adults and adolescents 12 years of age and older.
- *Limitations of Use*: Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

Recommended Pretreatment Evaluations and Immunizations

- Tuberculosis screening; preventive therapy for latent tuberculosis.
- Viral hepatitis screening (hepatitis B and C viruses)
- Lymphocyte and platelet counts; treatment should not be initiated if absolute lymphocyte count is < 500/mm^3 or platelet count is < 100,000/mm^3.
- Update immunizations according to current guidelines.
- Liver function tests. Treatment is not recommended in patients with severe (Child-Pugh C) hepatic impairment.

Dosage Regimen and Dosage Form Under Review

- 50 mg orally once daily with or without food.
- Capsules: 50 mg in bottles of 28

Recommended Evaluations After Initiation of Treatment

- Lymphocyte and platelet counts 4 weeks after starting treatment then according to routine patient management.

Dosage Modifications

- Platelet count < 50,000/mm^3: Discontinue treatment.
- Lymphocyte count < 500/mm^3: Interrupt therapy.
- Treatment interruptions for < 6 weeks are not expected to result in significant loss of regrown scalp hair.

Efficacy Considerations

- No active-controlled trials have been performed.
- ALLEGRO, a 24-week, phase 2b/3, dose- and placebo-controlled randomized clinical trial (RCT) with a 24-week extension, showed the efficacy of ritlecitinib in achieving a Severity of Alopecia Tool (SALT) score ≤ 20 (≥ 80% scalp hair coverage) at Week 24.[ii] Dosage regimens that included a loading dose showed earlier responses but similar Week-48 responses, greater decreases in lymphocyte counts, and more frequent adverse events including lymphopenia and rash, relative to those without a loading dose.**Error! Bookmark not defined.**
- A long-term study (ALLEGRO-LT) is ongoing.
- A phase 2 RCT and its maintenance, withdrawal, and re-treatment extension study provided supportive evidence of efficacy and suggested that continuous therapy should be considered to maintain hair regrowth.[iii,iv]

Phase 2b/3 Randomized Clinical Trial

Methods

- Table 1 summarizes the methods of the phase 3 RCT.

Table 1 Method of Phase 3 RCT

Topic	ALLEGRO
Study Design	24-week (4-week loading, 20-week maintenance) MN DB DC DD PC RCT; stratification by scalp hair loss (targeted about 40% of patients with alopecia totalis or alopecia universalis) and age (target 15% of patients in 12–17 year-old age group) Significance level of 0.00125 Followed by 24-week extension study
Major Entry Criteria	*Inclusion:* Age ≥ 12 years Alopecia areata with no other etiology for hair loss ≥ 50% scalp hair loss (SALT ≥ 50) including alopecia totalis and alopecia universalis and no evidence of terminal hair regrowth within 6 months Current episode of hair loss ≤ 10 years *Exclusion:* Clinically significant depression Acute, fluctuating, or progressive auditory conditions Previous use of JAKI or non-B-cell selective lymphocyte-depleting agent (e.g., alefacept, alemtuzumab) Use of any B-cell-depleting agents (e.g., rituximab) within previous 6 months or five half-lives Use of other biologic immunomodulators within previous 12 weeks or five half-lives Use within previous 8 weeks of other systemic treatments that could affect alopecia areata History of disseminated herpes zoster, disseminated herpes simplex, or recurrent localized, dermatomal herpes zoster
Interventions	*2:2:2:2:1:1:1 randomization* Loading dose of 200 mg QD for 4 weeks then 50 mg QD (200 / 50 mg) Loading dose of 200 mg QD for 4 weeks then 30 mg QD (200 / 30 mg) 50 mg QD 30 mg QD 10 mg QD (not included in placebo statistical comparisons) Placebo for 24 weeks then ritlecitinib 200 mg QD for 4 weeks then 50 mg QD (placebo / 200 / 50 mg) Placebo for 24 weeks then ritlecitinib 50 mg QD (placebo / 50 mg)
Key Efficacy Measures	*Primary*: SALT ≤ 20 response at Week 24 *Secondary*: SALT ≤ 10 response at Week 24

Sources: ii, v

Results

- The study population of 718 patients had a mean age of 33.8 years with 85% of patients ≥ 18 years old. Overall, 39% of patients were male, 68% White, 26% Asian, and 4% Black or African American, and 46% had alopecia totalis or alopecia universalis. Prior use of topical or systemic immunomodulators for AA was not reported.
- Efficacy data for the eventually approved 50-mg daily dose without a loading dose are summarized in Table 2.

Table 2 Key efficacy results from ALLEGRO, Week 24

Outcome	Ritlecitinib 50 mg QD	PBO	Relative Risk (95% CI)	AAE (95% CI)	NNT (95% CI)	Q
SALT ≤ 20, n/N (%)	29/124 (23.4)†	2/130 (1.5)	15.2 (3.7, 62.4)	218 (146, 302)	5 (4, 8)	L[α]
SALT ≤ 10, n/N (%)	17/124 (13.7)	2/130 (1.5)	8.9 (2.1, 37.8)	122 (63, 195)	9 (6, 18)	L[α]

Sources: ii, **Error! Bookmark not defined.**

AAE, Anticipated absolute effect for achieving the outcome per 1000 patients; **CFB**, Change from baseline; NNT, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence

† P < 0.0001. The level of statistical significance used for the FDA was α = 0.00125.

[α] Downgraded for indirectness (not a clinical outcome) and imprecision (wide CIs and/or optimal information size not met).

- Secondary efficacy results:
  - Patient Global Impression of Change score of moderately improved or greatly improved at Week 48 was significantly better on ritlecitinib 50 mg QD than placebo: 49.2% vs 9.2% (difference 40.0; 95% CI 28.8, 51.1).
- Subgroup Analyses
  - Subgroup analyses by disease severity showed a greater SALT ≤ 20 treatment effect with ritlecitinib 50 mg QD in patients without (25/69, 36.2%; difference [95% CI] vs placebo, 33.4 [21.7, 45.6]) vs those with (4/55, 7.3%; 7.3 [1.0, 17.3]) alopecia totalis / alopecia universalis.
  - No subgroup response predictors were observed in analyses by age (adolescents 12–17 years vs adults ≥ 18 years).[ii] No SALT ≤ 20 treatment benefit was seen in the subgroup of patients ≥ 65 years; however, event numbers were small (1/3, 33.3%; 95% CI, –46.0, 69.7).**Error! Bookmark not defined.**

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings**: Serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.
- **Contraindications**: Known hypersensitivity to ritlecitinib or its excipients.
- **Other Warnings / Precautions**: Hypersensitivity, laboratory abnormalities (decreased lymphocytes and platelets, increased liver enzymes and blood creatine phosphokinase [CPK]), avoid use of live vaccines during or shortly before treatment.
- **Common Adverse Events (≥ 1%):** Headache, diarrhea, acne, rash, urticaria, folliculitis, pyrexia, atopic dermatitis, dizziness, blood CPK increased, herpes zoster, decreased red blood cell count, stomatitis.

Safety Results from ALLEGRO

- No treatment differences between ritlecitinib 50 mg QD and placebo were observed in rates of serious adverse events, discontinuations due to adverse events, and adverse events.
- Five serious infections (empyema, sepsis, appendicitis, and diverticulitis) were reported in 4 ritlecitinib patients.
- Mortality, Malignancies, Major Adverse Cardiovascular Events (MACE), and Thrombosis: There were no deaths and no MACEs. Two patients developed breast cancer and one patient developed pulmonary embolism in the ritlecitinib treatment groups.[iii]
- Nonserious herpes zoster occurred in 8 patients among the three higher or loading dose (50 mg, 200 / 30 mg, and 200 / 50 mg) ritlecitinib groups.
- Neurologic events of interest occurred in 30 patients, mainly (in 25 patients) up to Week 24. Six patients had nonserious sensorineural hearing loss on protocolled audiologic testing (not spontaneously reported). None of the events had evidence suggestive of central hearing disorders.
    - Hearing loss in humans is not mentioned in prescribing information.[i]
    - In dog studies, dose-related reversible axonal dystrophy and reversible hearing loss occurred at 33 times the maximum recommended human dose.[i] The mechanism of axonal dystrophy in dogs was not identified but preliminary evidence showed that it was not directly caused by JAK3 or TEC family kinase inhibition.[i]
- The incidence of increased CPK was higher among ritlecitinib groups (range 1.2% to 3.7%) than placebo (0.5%). No cases of rhabdomylosis were reported.

Drug–Drug Interactions

- **Certain CYP3A substrates**: Consider additional monitoring and dose adjustment of CYP3A substrate.
- **Certain CYP1A2 substrates**: Consider additional monitoring and dose adjustment of CYP1A2 substrate.
- **Strong CYP3A inducers**: Avoid.

Evidence Gaps

- Health-related Quality of Life
- Functional ability / Disability
- Patient Satisfaction

Network Meta-analyses

- A network meta-analysis of nine RCTs (N = 1812) evaluated JAK inhibitors, dupilumab and apremilast as monotherapy in adults with alopecia areata.[vi] The relative effects of US-marketed AA agents based on indirect comparisons are summarized in Table 3. The quality of evidence for the indirect treatment comparisons was not provided.

Table 3 Relative Efficacy and Safety of AA Treatments (Week 24): Network Meta-analysis

Drug Ranked Best	Drug Ranked Worst	RITLE Superior to	RITLE Similar to	RITLE Inferior to
At least a 50% reduction in SALT score (SALT–50)				
Ruxolitinib	Apremilast	Ruxolitinib cream Apremilast	Baricitinib (2 or 4 mg) Dupilumab	Ruxolitinib Tofacitinib

Drug Ranked Best	Drug Ranked Worst	RITLE Superior to	RITLE Similar to	RITLE Inferior to
At least 75% reduction in SALT score (SALT–75)				
Ruxolitinib	Placebo / Vehicle	—	Baricitinib (2 or 4 mg) Dupilumab	Ruxolitinib Tofacitinib
At least 90% reduction in SALT score (SALT–90)				
Ritlecitinib	Placebo / Vehicle	Baricitinib (2 mg QD)	Baricitinib (4 mg) Ruxolitinib cream 1.5% Dupilumab	—
Discontinuations due to adverse events				
Ritlecitinib	Apremilast	—	Dupilumab Apremilast	—

Drug dosage regimens, all for 24 weeks except as noted: Apremilast 30 mg BID; baricitinib QD; dupilumab SC QW; ritlecitinib 200 mg QD x 4 weeks then 50 mg QD x 20 weeks; ruxolitinib 20 mg BID; ruxolitinib cream 1.5% BID; tofacitinib 5 mg BID
Abbreviations: RITLE, Ritlecitinib

Other Considerations

- **Onset of effects** (earliest significant treatment difference): Statistical differences were not assessed before Week 24. A treatment difference based on non-overlapping 95% CIs between ritlecitinib 50 mg QD and placebo occurred at Week 18.
- **Duration of an adequate therapeutic trial** (time to plateau in maximal SALT ≤ 20 response): The duration of an adequate therapeutic trial seems to be after 48 weeks of treatment based on SALT ≤ 20 response for scalp hair; although rates were leveling off by 48 weeks, a plateau was not reached.[ii,] **Error! Bookmark not defined.**
- **Durability of response**: The phase 2 single-blind extension study showed that, in 22 ritlecitinib active responders during the double-blind study period who were switched to placebo in the withdrawal study period, the median time from the end of the double-blind period to re-treatment was 16.1 weeks. Active responders were patients who achieved ≥ 30% improvement in SALT score from baseline to Week 24. Patients received placebo until there was > 30% loss of hair that was regrown during the double-blind period, at which time 24 weeks of ritlecitinib was restarted.

Other Therapeutic Options

- No society guidelines include dual JAK / TEC inhibitors.
- The only other systemic agent FDA approved for treatment of severe AA in adults is baricitinib. Ritlecitinib is also approved for treatment of severe AA in adolescents ≥ 12 years of age, whereas baricitinib is approved only in adults.
- Ritlecitinib and baricitinib differ in certain aspects of their safety profiles (Table 3).

Table 4 Safety profiles of ritlecitinib vs baricitinib

Safety Issue	Baricitinib	Ritlecitinib
Boxed Warnings	Serious infections, mortality, malignancy, MACE, and thrombosis	Serious infections, mortality, malignancy, MACE, and thrombosis
Renal Impairment	Modify dosage for mild (eGFR 60 to < 90 ml/min/1.73 m^2) or moderate	—

Safety Issue	Baricitinib	Ritlecitinib
	(eGFR 30 to < 60 mL/min/1.73 m^2) renal impairment Not recommended in severe (eGFR < 30 mL/min/1.73 m^2) renal impairment	
Severe (Child-Pugh C) Hepatic Impairment	Not recommended	Not recommended
Absolute Lymphocyte Count (ALC) < 500/mm^3	Initiation of therapy is not recommended Interrupt therapy; may restart when the count is above this value	Initiation of therapy is not recommended Interrupt therapy; may restart when the count is above this value
Absolute Neutrophil Count (ANC) < 1000/mm^3	Initiation of therapy is not recommended Interrupt therapy; may restart when the count is above this value	—
Hemoglobin (Hg) < 8 g/dL	Initiation of therapy is not recommended Interrupt therapy; may restart when the count is above this value	—
Platelet Count (PLT)	—	Initiation of therapy is not recommended if < 100,000/mm^3 Discontinue therapy if < 50,000/mm^3
Increased Liver Enzymes / DILI	Interrupt therapy if ALT or AST increases and DILI is suspected; may restart when DILI is excluded	Interrupt therapy if ALT or AST increases and DILI is suspected; may restart when DILI is excluded
Increased Creatine Phosphokinase (CPK)	—	Associated with increased blood CPK; no specific recommendations for monitoring or management.
Drug Interactions		
Strong OAT3 inhibitors (e.g., probenecid)	Modify dosage	—
Sensitive CYP3A Substrates† (e.g., midazolam)	—	Consider additional monitoring and dosage adjustment of the substrate
Sensitive CYP1A2 Substrates† (e.g., caffeine)	—	Consider additional monitoring and dosage adjustment of the substrate
Strong CYP3A Inducers (e.g., rifampin)	—	Not recommended

DILI, Drug-induced liver injury; MACE, Major adverse cardiovascular events; OAT, Organic anion transporter
† Sensitive substrates refer to those that may lead to serious adverse events when there are small changes in their concentration

- Systemic corticosteroids are considered as first-line, short-term therapy for severe AA to halt disease progression.
- Systemic corticosteroids and other agents (e.g., tofacitinib, ruxolitinib, conventional immunomodulators) have less evidence than baricitinib and ritlecitinib, and are used off-label. For more information, refer to the *Baricitinib OLUMIANT in Alopecia Areata Monograph* available at the PBM SharePoint.

Projected Place in Therapy

- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials were available, low-quality evidence from a placebo-controlled trial supports the use of ritlecitinib 50 mg QD in adult and adolescent patients with severe AA. The efficacy of ritlecitinib in patients with an inadequate response or loss of response to JAK inhibitor therapy is uncertain because the study population had no prior exposure

to JAK inhibitors. The study population's prior exposure to topical and other systemic AA treatments is also uncertain. The SALT ≤ 20 response benefit was small and its clinical meaning in terms of quality of life or psychosocial function is uncertain. The overall SALT ≤ 20 efficacy of ritlecitinib in patients with alopecia totalis or alopecia universalis may be negligible. Potential advantages of ritlecitinib vs baricitinib are a different mechanism of action, no dosage adjustment needed in renal impairment, lack of adverse ANC and Hg effects, and different drug-interaction profile. Whether ritlecitinib has a more rapid onset or better overall safety and tolerability profile over other JAK inhibitors is uncertain, although inconclusive, indirect comparisons from network meta-analyses based on SALT–75 and SALT–90 suggest that ritlecitinib might be similar to or more effective than baricitinib 2 mg and similar to baricitinib 4 mg. The ALLEGRO study results pertain to a multinational, middle-aged patient population which consisted of mostly female adults with severe AA (≥ 50% scalp hair loss) without evidence of terminal scalp hair regrowth within the previous 6 months and whose current episode of hair loss was ≤ 10 years in duration. The study population was enriched with patients who had alopecia totalis or alopecia universalis. Black / African American patients were underrepresented.

- **Potential Place in Therapy in VHA**. Ritlecitinib may be an alternative to (at the same level as) baricitinib in patients with severe AA (≥ 50% scalp hair loss).

Prepared December 2023.

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